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CHOLINESTERASE LEVELS IN THE SKIN IN CHOLINOGENIC URTICARIA AND PRURITUS.

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IN 1936 Grant, Bruce Pearson and Comeau published an account of observations on a type of urticaria provoked by emotion, by exercise, by warming the body or by the subcutaneous injection of carbachol. They demonstrated also that local whealing in these patients can be produced by the introduction iontophoretically into the skin of pilocarpine or of carbaminoyl choline. They found acetylcholine, introduced in this way into the skin, to be uncertain in its action, only occasionally producing whealing, but the addition of eserine, itself with no effect on the skin in the concentrations used, caused an urticarial response. They concluded that the urticaria in these patients is brought about by an abnormal reaction of the skin to normal amounts of acetylcholine released at nerve-endings. The disorder has therefore subsequently been termed "cholinogenic urticaria" by American workers (Hopkins, Keston and Hazel, 1938). An apparently related condition, termed "cholinogenic pruritus" by Nomland (1944), has also been described, in which the patient experiences pruritus without urticaria, brought on, again, by emotion, exercise or heat and also, it is claimed, provoked by mecholyl.

A possible mechanism underlying the abnormal reaction of the skin to acetylcholine, postulated by Grant *et al.* (1936), might be reduced activity of cholinesterase in the skin, as suggested by Peters and Silverman (1946), due either to a deficiency of the enzyme in this tissue, or to the presence of an inhibitor. In regard to normal skin Thompson and Whittaker (1944) had earlier shown that this enzyme is present in the human, and this work was extended by Magnus

and Thompson (1954) who carried out a survey of the cholinesterase activity in 54 samples of normal human skin. They found that although skin contains both types of cholinesterase, pseudocholinesterase is present in considerably greater amount than the true cholinesterase. Pseudocholinesterase activity per unit weight of skin was found to be greater in the female than in the male; specimens of skin from the anterior abdominal wall, the loin, the interscapular region, the inguinal region, the forearm, the chest, the finger and the scrotum were studied, but no marked differences in activity in different regions of the body surface were found in specimens from either sex. Magnus and Thompson (1954) also reported that the pseudocholinesterase levels in skin taken from two male subjects with cholinogenic urticaria (specimens taken from the scapular and forearm regions respectively) were considerably below the level in normal skin.

The present paper describes assays carried out on a further series of patients with cholinogenic urticaria, so-called "cholinogenic pruritus", and other conditions manifesting whealing. In addition, patients with a variety of dermatoses, and one with polycythaemia rubra vera (but apparently normal skin) in which pruritus was precipitated by heat, exercise and emotion, were studied in the same way. As itching is so often precipitated or aggravated in these circumstances in inflamed skin, only patients in which such symptoms were a leading feature were included. The response of some of these patients to acetylcholine injected into the skin has also been studied, and the results considered together with the cholinesterase assays.

EXPERIMENTAL.

Materials.—Samples of skin were taken from 5 patients with cholinogenic urticaria (4 males, 1 female), 2 patients with cholinogenic pruritus (1 of these with a history suggesting that he had previously suffered from cholinogenic urticaria), 5 with dermatographia (one, a female, who also complained of itching excited by heat and exercise), 5 with chronic idiopathic urticaria and 2 with urticaria pigmentosa. The following patients were also studied on account of their history of itching provoked by heat, exercise or, in some cases, emotion: 5 with prurigo of unknown cause, 1 with lichenified dermatitis of the shoulders associated with rosacea, 1 with lichenified seborrhoeic dermatitis, 1 with polycythaemia rubra vera and apparently normal skin. A biopsy was also taken from a female patient with atopic dermatitis. One case of urticaria provoked by exercise was also included, although in this patient the condition did not fall clinically into the group of cholinogenic urticaria, since the rash was not evoked by heat, emotion or cholinergic drugs, but only after prolonged exercise. In addition a patient with localized heat urticaria was studied; in this patient whealing was provoked only in the heated area of skin, e.g. when the forearm was immersed in water as hot as could be comfortably tolerated for 10–15 min., a confluent wheal appeared affecting only the immersed skin.

Skin biopsies.—Skin biopsies were taken from either the scapular, inguinal, anterior chest or forearm regions. 1% cetrimide was used as the skin cleansing agent, and 2% procaine as the local anaesthetic. Where skin was pathologically thickened, e.g. by lichenification, the biopsy was taken from an area clinically normal in appearance but as near as possible to the lesions. It was felt that assay of skin thickened by oedema,

hyperkeratosis, acanthosis, etc. might give lower cholinesterase values expressed on a weight basis as compared with the normal.

Estimation of cholinesterase activity.—After scraping away subcutaneous fat and connective tissue the specimen was minced with sharp scissors into a fine pulp. Cholinesterase activity was then estimated at 38° C. and at pH 7.4, using weighed amounts of minced skin (between 50–150 mg. skin/Warburg flask). Butyrylcholine perchlorate (0.03 M), dissolved in 0.025 M sodium bicarbonate solution, was used as a selective substrate for pseudo-cholinesterase. The free acid released from the substrate by the action of the cholinesterase liberates CO₂ from the bicarbonate medium ; the volume of CO₂ set free is then measured using the Warburg technique as modified by Ammon (1933). All measurements were done in duplicate, and corrected for non-enzymic hydrolysis of the substrate. Activity is expressed as $\mu\text{l. CO}_2/\text{g. skin (wet wt.)}/\text{hr.}$ Estimations of true cholinesterase activity were not done because of the low activity of this enzyme in normal skin.

Intradermal tests.—The sensitivity of the patient's skin to acetylcholine was tested by injecting intradermally 0.05 ml. of a 1 : 10,000 solution of acetylcholine chloride (Roche Ltd.) in sterile 0.9% saline. Timed measurements were made of the maximal size of the flare, and the times of their persistence and subsidence noted. 26 normal persons were also studied in the same way

RESULTS.

Skin cholinesterase measurements.—The levels of skin cholinesterase found in the patients suffering from these various urticarial or itchy dermatoses are listed in Tables 1 and 2 (see also Fig. 1). It will be seen that, for biopsies from

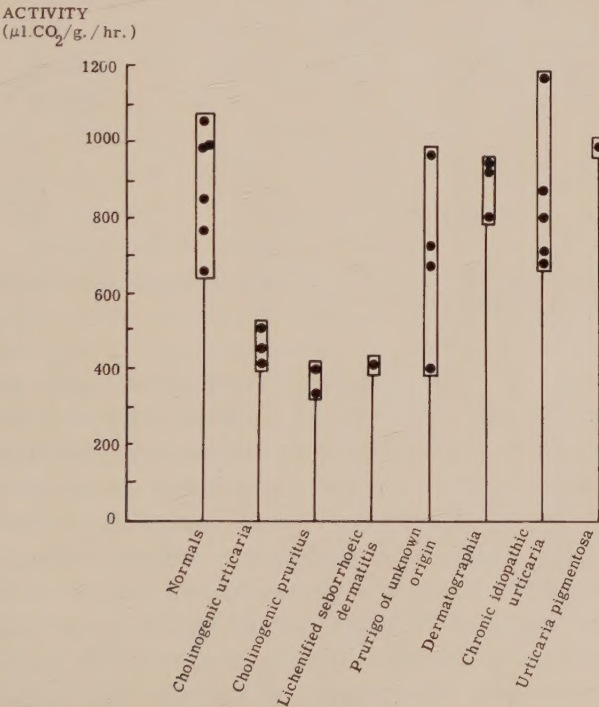


FIG. 1.—Pseudo-cholinesterase levels in skin biopsies from males (scapular region only).

TABLE I.—*Skin Cholinesterase Levels in Male Subjects Suffering from Various Urticarial or Itchy Dermatoses.*(Activity expressed as $\mu\text{l.CO}_2/\text{g. skin/hr.}$)

Condition.	Inguinal biopsy.	Anterior chest wall biopsy.	Scapular biopsy.	Forearm biopsy.
Normal* . . .	$\left\{ \begin{array}{c} 664 \\ 959 \\ 628 \\ 975 \\ 1015 \\ 1024 \end{array} \right\}$ 878	$\left\{ \begin{array}{c} 603 \\ 610 \end{array} \right\}$ 607	$\left\{ \begin{array}{c} 657 \\ 1056 \\ 762 \\ 985 \\ 849 \\ 990 \end{array} \right\}$ 883	$\left\{ \begin{array}{c} 799 \\ 723 \\ 1187 \\ 678 \\ 980 \end{array} \right\}$ 872
Cholinogenic urticaria . . .	— .	— .	$\left\{ \begin{array}{c} 408 \\ \dagger 508 \\ 453 \end{array} \right\}$ 456	$\left\{ \begin{array}{c} 343 \\ \dagger 350 \end{array} \right\}$
Cholinogenic pruritus . . .	— .	— .	$\left\{ \begin{array}{c} 338 \\ 401 \end{array} \right\}$ 370	—
Dermographia . . .	— .	— .	$\left\{ \begin{array}{c} 802 \\ 947 \\ 932 \end{array} \right\}$ 897	—
Chronic urticaria . . .	— .	— .	$\left\{ \begin{array}{c} 873 \\ 800 \\ 685 \\ 713 \\ 1173 \end{array} \right\}$ 849	—
Urticaria pigmentosa . . .	— .	— .	985	710
Prurigo	508	— .	$\left\{ \begin{array}{c} 400 \\ 675 \\ 724 \\ 963 \end{array} \right\}$ 782	—
Polycythaemia rubra vera . . .	— .	777 .	— .	—
Lichenified seborrhoeic dermatitis . . .	— .	— .	410 .	—

* Normal values taken from Magnus and Thompson (1954).

† Biopsies from the same patient.

any of the selected areas of skin, the cholinesterase levels are appreciably lower than normal in all 7 patients suffering from either cholinogenic urticaria or pruritus. On the other hand biopsies from male patients with dermatographia, chronic idiopathic urticaria, urticaria pigmentosa or polycythaemia rubra vera each showed levels within the normal range. The case of lichenified seborrhoeic dermatitis and also 2 of the male patients suffering from prurigo gave levels appreciably below the normal range; one of the 2 females with dermatographia and the one with lichenified dermatitis also showed low levels of cholinesterase activity. The patients with localized heat urticaria and with non-cholinogenic urticaria precipitated by exercise had normal levels. The patient with atopic dermatitis also showed a value within the normal range.

TABLE II.—*Skin Cholinesterase Levels in Female Subjects Suffering from Various Urticarial or Itchy Dermatoses.*
(Activity expressed as $\mu\text{l}.\text{CO}_2/\text{g. skin/hr.}$)

Condition.	Scapular biopsy.
Normal*	$\left\{ \begin{array}{l} 879 \\ 978 \\ 913 \\ 1008 \\ 1006 \end{array} \right\} 957$
Cholinogenic urticaria	660
Prurigo	1181
Atopic dermatitis	989
Lichenified dermatitis and Rosacea	773
Dermographia	613
	1020
Localized heat urticaria	955
Non-cholinogenic urticaria precipitated by exercise	974

* Normal values taken from Magnus and Thompson (1954).

Intradermal tests.—0.05 ml. of 1 : 10,000 acetylcholine chloride (ACh) in 0.9% sterile saline injected intradermally into the forearm and scapular areas in 18 out of 26 normal persons produced little or no reaction apart from a wheal due to the injected fluid. Eight normal subjects showed a faint erythema of rapid onset often affecting a wide area, i.e. discernible within 2 or 3 seconds of the injection or while it was being completed; this usually faded in 5–10 seconds. As stated by Lobitz and Campbell (1953), it is probably of axon reflex origin. Also seen in 6 normal subjects was an erythema that developed later and more slowly, i.e. commenced within about a minute after completion of the injection, reached a maximal area and intensity 2 to 4 min. later, then faded completely by 5 to 10 min., or left sometimes a more persistent but indistinct local redness at the injection site. In 3 patients with cholinogenic urticaria (one was not tested) and the 2 designated cholinogenic pruritus this erythema of relatively delayed onset and longer duration following intradermal ACh lasted 40–60 min., and the area affected was considerably larger than that seen in normal subjects. One of the patients with cholinogenic urticaria produced satellite wheals within the area of erythema. The extent of the reaction in these patients however was found to vary greatly on repeated testing, and in a fourth patient with cholinogenic urticaria the delayed erythema resembled that seen in some normal subjects, both in size and persistence. In the remaining 23 patients with other dermatoses, including the patient with urticaria precipitated only by exercise (non-cholinogenic), the response to this test was indistinguishable from that seen in normal subjects, except in some of the dermatographic subjects, where control injection with normal saline indicated that when their skin reacted abnormally, it was due to the trauma of injection and not to the action of ACh. The patient with localized heat urticaria was not tested intradermally.

DISCUSSION.

Since, as the present findings indicate, the skin in patients with cholinogenic urticaria is found to have a reduced pseudo-cholinesterase activity, a possible mechanism underlying the formation of the lesions in this condition might be an abnormal accumulation of ACh in the skin, leading to pathological dilatation of the skin blood-vessels. With the present evidence available it is not possible to state in what structure of the skin the reduced cholinesterase activity lies. Herxheimer (1954), by provoking an attack in a patient with cholinogenic urticaria in which previously a temporary block of the cervical sympathetic chain had been effected on one side, stated that urticarial lesions developed mostly in the skin area unaffected by the block. This result seems to support the view that in this disorder the pathway of the nervous mechanism concerned lay in the sympathetic nervous system. In regard to the results of the intradermal tests, Lobitz and Campbell (1953) suggested that the erythema of relatively delayed onset from intradermal ACh in normal subjects was due to the direct action of ACh on the dermal vessels. Release of H-substance may however be the cause. The work of Moynahan (1952) seems to support this. In a few experiments we have been unable to influence convincingly the delayed erythema of ACh by giving ACh mixed with atropine or, in one case, ACh intradermally and atropine subcutaneously; further, the phenomenon was not enhanced by the pseudo-cholinesterase inhibitor TEPP (tetra-ethyl pyrophosphate) given intradermally. If the delayed erythema, which was so prolonged in some of our patients with cholinogenic urticaria, is ultimately due to histamine release, this would be in harmony with the suggestions of Grant *et al.* (1935).

In view of the report by Morgan (1953) that the serum cholinesterase in 3 patients suffering from cholinogenic urticaria was low, we have also determined the serum cholinesterase levels in our 4 male patients with cholinogenic urticaria and the 2 with cholinogenic pruritus; in every case the levels were within the normal range.

The position of cholinesterase activity in regard to the mechanism of the cholinogenic pruritus of Nomland (1944) and the aggravation of itching in inflamed skin by heat, exercise and emotion is much less clear on the basis of our results. Of the two patients we have designated as cholinogenic pruritus, both with low cholinesterase values in the skin, one was possibly a mild example of cholinogenic urticaria. In one female patient and 4 males with marked "cholinogenic itching" associated with either lichenified dermatitis or prurigo, the cholinesterase activity in the areas affected by itching was low; however, these low values may have been due to the fact that the biopsy specimen included skin pathologically thickened by oedema which would reduce the activity when expressed on a weight basis. Nevertheless, one female with dermatographia

and a strong history of cholinogenic itching gave a low cholinesterase value. It is possible that this patient had both dermatographia and the Nomland cholinogenic pruritus, for all other patients with dermatographia alone gave values within normal limits. The relation on the one hand of cholinogenic itching and its possible association with cholinesterase activity in the skin with, on the other hand, the recent report by Shelley and Arthur (1955) in regard to the role of proteolysis and itching, remains yet to be determined.

SUMMARY.

The level of pseudo-cholinesterase has been measured in biopsy specimens of skin taken from patients suffering from cholinogenic urticaria, "cholinogenic pruritus", and other dermatoses.

The sensitivity of the skin of these patients to intradermally injected acetylcholine has also been studied.

The pseudo-cholinesterase activity of the skin was found to be low in cases of cholinogenic urticaria and pruritus.

The significance of this finding is discussed in relation to the sensitivity of the skin to acetylcholine and to the general problem of the aetiology of these conditions.

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LOCALIZATION OF NON-SPECIFIC CHOLINESTERASE IN MEISSNER'S CORPUSCLES IN HUMAN SKIN.

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THE histochemical technique of Koelle (1951) permits the identification of two kinds of cholinesterases (ChE's). The first is called specific ChE; it hydrolyzes the added substrate acetylthiocholine and its presence identifies the cholinergic type of innervation, as for example to the eccrine and apocrine sweat glands (Hurley *et al.*, 1953), arteriovenous anastomoses (Hurley and Mescon, 1956), and the arrector pili muscles (Aavik, 1954). The second is called non-specific ChE; it hydrolyzes the added substrate butyrylthiocholine but its further significance is not known. It has been found in serum, capsular glial cells of sensory and autonomic ganglia, Schwann's sheath cells, lining cells of hepatic sinusoids, smooth muscle fibres, stellate cells and occasional ganglion cells of the ileum, groups of chemoreceptor cells in the carotid body, and in white and grey fibre tracts of the central nervous system (Koelle, 1951; Hurley *et al.*, 1953; Ord and Thompson, 1950.) This presence of the enzyme in a variety of cells (nerve, smooth muscle, lining, etc.) appears to indicate a non-specific biochemical role. Nevertheless since the enzyme is not generally distributed, it must apparently catalyze reactions restricted to certain cells, though not to certain kinds of cells.

Both types of ChE have been assayed in human skin (Magnus and Thompson, 1954) but hitherto only specific ChE has been localized about particular skin structures. This report presents the first evidence of the localization of non-specific ChE in a special structure of the skin, namely, the tactile corpuscles of Meissner. These corpuscles (Fig. 1) are specialized nerve endings found in about one-fourth of the dermal papillae of the volar skin of the palms and soles, fingers and toes, and portions of the external genitalia. They are elliptical structures, 40–100 μ in thickness, which contain a core of flattened "tactile" cells (Greep, 1954) arranged transversely to the long axis of the corpuscle. A capsule and its transverse septae of connective tissue are prominent morphologic features also. One to five medullated nerve fibres enter the lower end of the corpuscle, lose their myelin and pursue a spiral course often parallel to the tactile cells. These fibres terminate between and upon the tactile cells.

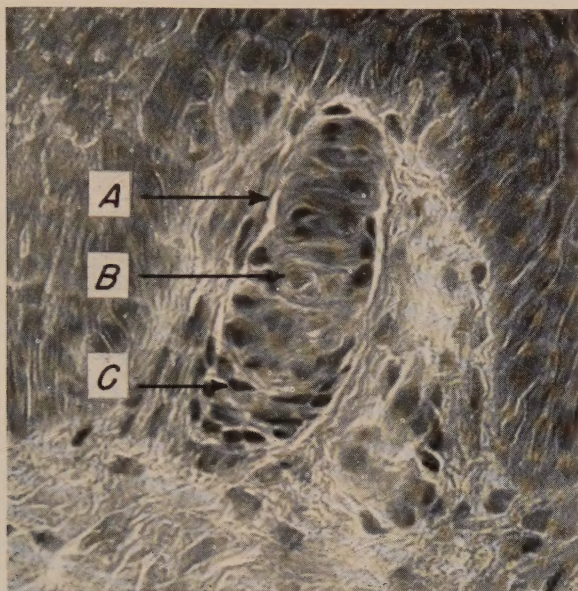


FIG. 1.—Meissner tactile corpuscle of human volar skin. Elliptical shape of Meissner corpuscle high in dermal papilla is apparent. Connective tissue capsule (A) and nucleus of transverse connective tissue lamella (C) are characteristic features. Note faintly-stained "tactile" cells (B) near and upon which fine nerve fibrils terminate. H. & E. $\times 530$.

EXPERIMENTAL.

Punch biopsies of the palm or volar pad of the great toe of seven healthy white male volunteers (21–25 years of age) were obtained after block anaesthesia with 1% procaine. Fresh frozen sections, 10μ thick, were placed on glass slides and carried through the histochemical method of Koelle (1951) for the localization of specific and non-specific cholinesterase activity. Acetylthiocholine and butyrylthiocholine were used as substrates and the tissues incubated at 37.5°C . for 15, 30 or 60 minutes. Diisopropylfluorophosphate, in a concentration of 10^{-10} M , was employed to inhibit selectively the non-specific ChE of the appropriate sections. Sections were counter-stained alternately with eosin or with haematoxylin and eosin.

RESULTS.

Moderate to high concentrations of non-specific cholinesterase, but not of specific ChE, were found in the corpuscles of Meissner but it was difficult to be certain of its precise localization within the corpuscles. In general the enzyme was oriented transversely with some areas of the corpuscles unstained or very lightly stained (Fig. 2, A). Many of the unstained areas, however, were found by counterstaining with haematoxylin and eosin to be nuclei of the connective

tissue capsule and septae (Fig. 2, B). Nuclei of the "tactile" cells, which stain poorly with haematoxylin (Fig. 1), could account for the absence of the enzyme within other areas of the corpuscle. No nerve fibres within or leading to the end-organ were outlined. Non-specific ChE was not detected in any other structures of the skin.

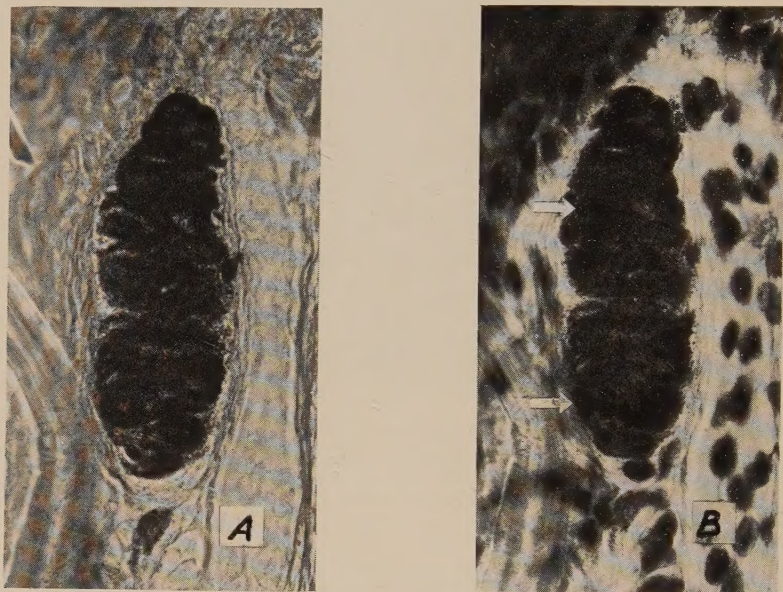


FIG. 2.—Non-specific cholinesterase in Meissner corpuscle of human skin. Dark material within corpuscle is copper sulphide precipitated at sites of ChE activity. Compare A (counterstained lightly with eosin) and B (same section counterstained with haematoxylin and eosin). Observe staining of connective tissue nuclei (arrows) in B. $\times 530$.

DISCUSSION.

Although Woollard (1936) has described fine nerve fibres arising from the neurofibrillae of Meissner's corpuscles and passing into the epidermis to form Merkel's discs, non-specific ChE was not detected in the epidermis adjacent to the corpuscles of Meissner or anywhere in the epidermis of the areas examined. Hebb and Hill (1955) found the enzyme in the core of the Pacinian corpuscles in the cat's mesentery and it is possible that it would be found similarly in the Pacinian corpuscles of human skin. We were unable to identify any of the latter endings in the specimens of skin examined here.

Because of their superficial location at the apex of the dermal papillae and of their high density in volar and labial skin where tactile sensation is most acute, it is generally considered that the corpuscles of Meissner subserve the sense of light touch (Rothman, 1954). The role that non-specific ChE plays in

this sense reception might possibly be disclosed by testing the effect of anti-cholinesterases, for even though non-specific ChE is not thought to be involved in the hydrolysis of acetylcholine (Koelle, 1951 ; 1955) some other ester might play a part. The information would be of value in the interpretation of results on the acclimatization of touch receptors to cold as reported by Mackworth (1954).

SUMMARY.

The localization of non-specific cholinesterase in the tactile corpuscles of Meissner in human volar skin is described.

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RADIOIODINE CLEARANCE AND HISTAMINE RESPONSE IN NORMAL HUMAN SKIN

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THE assessment of cutaneous circulatory efficiency by measurement of the rate of clearance of locally injected radioiodine was introduced by Kety (1949). Subsequently several groups of workers have employed this method in the clinical investigation of conditions involving impairment of blood flow. However, differences of opinion exist as to the significance and usefulness of the results obtained. Semple *et al.* (1951) in an investigation of blood flow in human muscle thought that the method was of little use. Likewise, Miller and Wilson (1951) considered that the test was insensitive as a measure of vascular conditions in skin and muscle. Other workers have found the method more valuable. Roswit *et al.* (1953), in an examination of skin damaged by radiation, decided that the clearance was a useful index of the volume of local blood flow. McNally *et al.* (1952) had reached the same conclusion as a result of an examination of the subcutaneous tissue of the leg. Moreover, in the field of plastic surgery Conway *et al.* (1951a) and Barron *et al.* (1951) considered the test to be a valuable guide to local circulatory conditions. Thus, although many workers have found the method to be reliable, there is no doubt that it is not as unambiguous an index of circulatory efficiency as could be wished.

This situation has focussed attention on the physiological mechanism of the test. Braithwaite *et al.* (1951, 1954) in an experimental and theoretical investigation of radioiodine clearance stressed the importance of available capillary surface area. They expressed the clearance rate in terms of capillary surface area and two other factors which depend, respectively, on the extracellular current through the tissues and the diffusion of sodium across the capillary wall. Buchanan *et al.* (1954) in a comparative study of clearance rate from the leg and forehead brought forward additional evidence in support of the significance of capillary surface area. However, Walder (1955) as a result of perfusion experiments in animals concluded that the rate of blood flow, and not the capillary surface area, was the factor which directly determined the clearance rate. He increased the venous back pressure while maintaining the blood flow at a constant level, and under these conditions found that the clearance was not materially altered.

In order to obtain further evidence in this connection we have made a series of paired measurements of radioiodine clearance rate and histamine wheal response. The employment of locally introduced histamine as a guide to cutaneous circulatory function was introduced by Starr (1928). de Takats (1931), Kramer (1940) and Conway *et al.* (1951*b*) have since reported favourably in this respect. However, the method of assessment of the response has proved variable. Some workers have directed attention principally to the flare, and others to the wheal, noting the time of appearance and the maximal area attained. Measurements of time are handicapped by practical difficulties in defining the onset of the reaction. In consequence we have confined our observations to quantitative determinations of the production of extra-capillary fluid. Initially, assessments were made of both maximal wheal area and height, and the resultant volume calculated. However, under the conditions of our experiments the calculated volume proved to correlate far less closely with radioiodine clearance than did wheal height alone. A possible explanation of this is that in normal subjects wheal height may represent an index of initial local extra-capillary fluid build-up prior to the effective operation of dispersal mechanisms which result not only in lateral spread of the fluid (measurable as area) but in considerable immeasurable loss from the deep surface of the wheal. Accordingly, we have adopted wheal height as the most suitable quantitative index of histamine induced extra-capillary fluid formation in normal subjects. However, this measure is clearly not applicable to subjects with greatly increased vascular flow rates; under these conditions dispersal factors may be so accelerated that fluid build-up is almost totally prevented.

METHOD

A very small volume of an isotonic solution of radioiodine bi-carbonate was injected into the superficial dermis, the amount required for convenient measurement being determined by means of a β -ray counter (EMH 2S). The physical half-life of radioiodine (^{131}I) is 15.1 hours: as a result the volume of solution corresponding to a given activity varies greatly from day to day. Accordingly, in order to maintain uniformity in respect of both volume and activity, the weekly consignment was used invariably over the same period. Furthermore, the injections were made by the same person on each occasion in an attempt to maintain their depth in the dermis as uniform as possible. Readings of the counting-rate meter were plotted on semi-logarithmic paper at half minute intervals, and the value for t obtained from the linear portion of the resultant curve (t = time in minutes taken for the counting rate to be halved).

As soon as these measurements were completed 0.05 ml. of a 0.1% aqueous solution of histamine acid phosphate was injected intradermally in the same

area, the maximal height of the resultant wheal later being recorded. This measurement was made most satisfactorily by means of a microscope with a calibrated vertical movement. Points were marked at the site of injection and to either side at such a distance as to be unaffected by the subsequent wheal. The height of the central point above or below that of the mean of the other two was determined by accurate focussing of the microscope before and after the development of the reaction. The difference between the two values represented the vertical dimension of the wheal.

The injection sites were confined to widely dispersed points on both upper and lower limbs. No attempt was made at inter-subject uniformity in this respect, since such considerations were irrelevant to the problem under investigation. Likewise, although the subjects were on all occasions investigated while at rest at an equable room temperature, rigid standardization was not enforced.

RESULTS AND DISCUSSION

Measurements were made on three normal male subjects aged 22, 30 and 41 years, the number of sites injected being 8, 7 and 11, respectively (Table I). When wheal height was plotted against the reciprocal of t the disposition of the points suggested a linear relationship between the two series of measurements in each subject. From these data the correlation coefficients and their probabilities were calculated to be: Subject 1: 0.85 ($P < 0.01$). Subject 2: 0.85 ($P < 0.025$). Subject 3: 0.76 ($P < 0.01$). Accordingly, we are justified in suspecting that under the conditions of our experiments both wheal height and radiosodium clearance rate are determined by the same property of the vascular system. However, this relationship applies only to the individual subject; comparisons between one subject and another fail to show the correlation. Thus it appears that there is an individual modifying factor.

TABLE I.

Subject 1.			Subject 2.			Subject 3.	
Wheal height (mm.).	$\frac{1}{t}$.		Wheal height (mm.).	$\frac{1}{t}$.		Wheal height (mm.).	$\frac{1}{t}$.
2.00	0.250	.	2.50	0.250	.	3.90	0.385
1.75	0.238	.	2.50	0.175	.	3.75	0.216
1.00	0.217	.	2.25	0.238	.	3.00	0.285
1.00	0.200	.	2.20	0.213	.	2.85	0.156
0.95	0.196	.	1.60	0.060	.	2.80	0.255
0.80	0.143	.	1.50	0.060	.	2.55	0.164
0.65	0.185	.	1.40	0.125	.	2.25	0.238
0.60	0.167	.	—	—	.	2.25	0.102
—	—	.	—	—	.	2.05	0.255
—	—	.	—	—	.	1.50	0.106
—	—	.	—	—	.	0.70	0.081

t = time in minutes taken for the counting rate to be halved.

It is generally considered that histamine induced whealing is due primarily to increased capillary permeability. Consequently, the amount of exudate formed per unit volume of dermis must be related to the total functional capillary surface area available for such permeability changes. It may be objected that there are many secondary factors playing contributory roles. Vascular flow rate is probably the most important of these. However, as we have previously pointed out, increases in this respect tend to diminish wheal height although accelerating radioiodine clearance. Such a relationship is the reverse of our findings. Accordingly, it seems improbable that variations of this factor in the individual subject are of significance under the conditions of our experiments (although inter-subject differences in this respect may well account for the observed lack of correlation on this plane). Therefore, the significant correlation between our two series of measurements may be interpreted as lending support to the concept that functional capillary surface area plays a fundamental role in determining the radioiodine clearance rate.

SUMMARY

Paired estimations of radioiodine clearance rate and histamine wheal height in normal skin under conditions of rest exhibit a significant correlation in the individual subject. It is considered that this relationship lends support to the concept of the fundamental importance of functional capillary surface area in determining the radioiodine clearance rate.

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THE VALUE OF X-RAY TREATMENT IN ECZEMA.

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In recent years there have been many interesting papers dealing with the effect of x-radiation on the normal skin of man and animals and with its penetration or absorption in various circumstances, but clinical studies concerning its therapeutic value in disease of the skin are scarce. Following a demonstration by Sulzberger, Baer and Borota (1952) that appreciable damage is rarely a sequel of x-ray treatment administered by dermatologists, Baer, Borota and Sulzberger (1952) went on to show, in the course of a follow-up of 1107 patients treated between 5 and 23 years previously for various skin diseases and of whom 637 had received x-rays in repeated fractional dosage, that the ratio of cures (meaning patients symptom-free when examined and not complaining of having had relapses in the interval) was in favour of x-ray treatment as 65 is to 42. In particular 31% of cases of psoriasis treated with x-rays had been cured as opposed to 17% of those who had had treatment with ointments alone. In chronic lichenified dermatitis the ratio was 45:25, in eczema 58:44, but in acne only 89:77. Only in the case of acne had the results been noticeably better with higher dosage than with small. But one cannot ignore the likelihood that the x-ray treatment schedules also involved, among other factors, a number of attendances at the clinic greater* than for patients having ordinary local treatment.

Crissey and Shelley (1952) recorded impressive results in lichen simplex chronicus, lichen planus and psoriasis but only equivocal benefit in eczema, contact dermatitis and acne. These workers deprecated simultaneous paired comparison "unless the lesion is continuous from one side to the other . . . because in clinical practice remission of a lesion on one side of the body and not on the other is often observed". Their series consisted of consecutive cases of the maladies mentioned, excluding only patients who had had x-ray before. The x-ray was administered to areas ranging from 1.9 to 6 cm. in diameter within selected lesions, and 100 r was given weekly for 4 weeks. (Although their photographs show that a circle has been drawn around the treated area, they do not explain exactly how they overcame the difficulties of making these small areas coincide exactly for the 4 exposures.) Then, having described the effects of x-ray on these small areas, they go on to discuss duration of improvement and

* This might just as well lead to a mithridatism as to a toxic dose (Balint, 1954) of doctor.

relapse rates without any mention of having subsequently treated larger areas ; this makes it difficult for the reader to relate their talk of patients cured for a time, etc., with the idea of a small island of healing within a larger patch of skin disease. Furthermore the authors find it necessary to postulate two types of response : " a consistent and significantly greater response within the radiated area " ; and " a steady progress towards healing in both radiated and control areas " .

I do not believe I am alone with the impression that in the days of the gas-tube the response of eczema to x-ray used to be excellent and that the only real difficulty was to resist the temptation to go on treating relapses ; but I cannot remember any successes with lichen planus. I also have the impression that during the war years, 1939-1945, I did not see a single soldier who was helped by x-ray and that since the war I have seen only one patient* with eczema, out of a grand total of about 50,000 new cases seen, who responded at all impressively. It seemed therefore worth while to try to find out by means of symmetrical paired comparison just how much therapeutic value can be ascribed to x-rays today.

The main experiment was based on a single dose of 150r delivered by a machine with the specification " K.X.10 with inherent filtration of 1 mm. Al. As operated at 100 k.v.p., a H.V.L. of 1.5 mm. Al. Output at 25 cm. f.s.d., 100 r per minute " . 150 r was taken as the standard because it seemed to be more or less what I and most of my colleagues are accustomed to prescribe, some of us limiting the treatment to a single dose and others giving 3 or 4 exposures at fortnightly intervals. The clinical material consisted of all patients seen initially by me at the hospital having subacute or chronic eczematoid dermatitis with symmetrical lesions on the extremities.

In addition a dozen consecutive cases received 250 r to one side only with no attempt to simulate treatment of the other ; in a few cases 5 weekly exposures of 50 r were given to one side and a single dose of 250 r preceded and followed by 2 dummy exposures to the other. In a few cases having extensive areas on the trunk, parts of the treated area were screened with lead rubber but no differences could be discerned. In a few cases in which the rash was on the face a dummy exposure was given first and 2 weeks later an exposure of 150 r, the results being compared and the patient asked to describe any differences noted. In one of these cases the patient was so pleased with the result of the dummy exposure that she wanted to buy the apparatus. Another was improved by the dummy

* Perhaps details of this exceptional and interesting case should be recorded. A Welsh brunette 24 years old had in 1948 extensive discoid eczema on the extremities and trunk characterized by unusually succulent lesions which tended to form, by confluence and spontaneous healing, gyrate patterns. Although these lesions could be made to disappear rapidly and completely with 100 r she did not find it worth her while, possibly because spontaneous improvement had begun to take place, to travel from Ffynnongroew to Manchester after the second relapse. Later she married and in due course brought along her first two babies who in succession had exceptionally severe infantile facial eczema. I did not see the father but I had no reason to disbelieve the denial of any family history of atopy on either side.

but remained untraceable after the real exposure. In one case the real exposure clearly did more good than the dummy. In 2 more the effects were equally good but in one of them the patient was aware of the difference—doubtless there would be a slight static “breeze”. Otherwise the results of these subsidiary experiments gave me no reason to believe that the choice of conditions for the main experiment was unfair to the form of treatment under investigation.

The method of symmetrical paired comparison was used in 89 cases, nearly all of which were of eczema having approximately symmetrical lesions so that a treated hand or upper extremity could be compared with its fellow which received either a dummy exposure* or, in a very few of the cases, no pretence of treatment. Where both upper and lower extremities were affected x-ray would be given to the right upper and left lower, the contralateral receiving dummy exposures of the same duration. Approximately half the cases were seen 10 days, and the rest 14 days after exposure, but many continued under observation for several months, the fruits of which will form the subject of a separate study. Of 89 cases treated, in only one (a case which was subsequently thought to be one of premycosis) were the changes distinct enough for it to be obvious where the tube had been centred. The other results are shown in Table I.

TABLE I.

Treated side healed, untreated side still active	.	.	.	.	.	.	.	.	3
“ “ improved, “ “ “ “	.	.	.	.	.	.	.	.	18
No change and no difference between the contrasted areas	.	.	.	.	.	.	.	.	26
Both sides healed	.	.	.	.	.	.	.	.	12
“ “ improved “ “ “ “	.	.	.	.	.	.	.	.	17
Treated side worse	.	.	.	.	.	.	.	.	7
Did not return, or no record of result	.	.	.	.	.	.	.	.	5
									88

Thus 88 cases of eczema were submitted to x-ray treatment under conditions of symmetrical paired comparison and, of the 83 in which the result was observed, no more than 21 showed any evidence of benefit. Of these the improvement could be regarded as unequivocal or substantial in only 5%, namely in the 3 cases in which the disease disappeared completely from the treated but was more or less unchanged on the untreated side (but in which the differences were insufficiently spectacular to provide photographic evidence) and just one of the cases designated as “improved on the treated side”. This designation was allowed to include any improvement appreciable either by patient or observer—for example, “looks very slightly better”, “feels better to the patient but looks much the same as the other side”, “urge to scratch less on the treated side”—and in none save the one case mentioned could the improvement have

* This precaution seems to have been unnecessary for patients treated on one side only were as a rule unable to remember which side had been treated.

been regarded as in proportion to the means used to obtain it. In 62 (74% of the total) x-rays appeared to have had no therapeutic effect at all.

Then how is it that most people believe x-ray to be highly effective in the treatment of eczema? Some even undertake in writing to cure industrial dermatitis with it! One of my colleagues who at first had kindly promised to co-operate in this investigation begged to be excused after a while because, he said, if he lost faith in x-rays he would have nothing left to offer his patients. Another colleague chooses to believe, in defiance of Occam, that x-ray treatment does not act locally but causes to be absorbed into the blood stream something which takes rather longer to act than anyone has hitherto supposed and depends for its success on being administered symmetrically. There is undoubtedly a good deal of resistance to the truth about x-ray, but I think the following observation may throw some light on the general belief that it is useful.

59 patients (not taking part in any of the above experiments) were seen during the same period at peripheral clinics on a Friday or a Saturday and referred for x-ray treatment to the Manchester Skin Hospital where they were seen again by me on the following Tuesday before having the treatment. 8 were found already to have healed completely, 34 were improved, 9 were unchanged or worse; in 8 cases there was no record. Every one of these patients had had skin trouble of long duration which had been showing no promise of improvement; and after making full allowance for the effects of the general practitioners' up-to-date treatment having been changed to lead lotion, it is impossible to escape the conclusion that the anticipation of receiving a dose of x-ray or perhaps just the visit to the big city does at least as much good as the radiation itself.

These seem to be the facts. Now what can be the explanation?

That the manufacturers of x-ray apparatus have been so successful in removing undesirable elements from the beam that it no longer has any therapeutic value? I have no doubt that some gas tubes complete with coil and mercury break still survive in museums, and could be used to test this hypothesis. Should it be correct, then the sooner we face the facts, take back our superficial x-ray therapy out of the hands of the radiologists, and design equipment suitable for dermatological use the better.

That the malady "eczema" has undergone a change? This hypothesis would be supported by the pretty general experience that nowadays fewer cases respond to tar ointment either.

That the material remedies at our disposal are fickle and unreliable in their effect on states the persistence of which may sometimes be due to non-material influences? Whatever may turn out to be the true answer to non-specific sickness in general or in particular we are not going to make any progress by claiming for our material remedies successes which are in reality due to lapse of time or at the best to some imponderable healing influence that we may

ourselves be fortunate enough to radiate. Disguise or suppression of the truth is bad for science, blunts our own powers of perception, and must even come under suspicion of being bad for the patient.

I have the greatest pleasure in acknowledging the helpful co-operation of the staff of the X-ray Department of the Manchester and Salford Hospital for Skin Diseases.

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A COMPARISON BETWEEN 9a-FLUOROHYDROCORTISONE AND HYDROCORTISONE IN THE TOPICAL TREATMENT OF CERTAIN DERMATOSES.

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IN the past few years certain derivatives of hydrocortisone have been made available. One of these compounds, 9a-fluorohydrocortisone acetate was first synthesized by Fried and Sabo (1953, 1954) by the insertion of the fluoro-atom at the 9a-position of hydrocortisone acetate. Goldfein *et al.* (1954) indicated from preliminary studies that 9a-fluorohydrocortisone acetate had approximately 25 times the therapeutic activity of cortisone when taken orally. Witten *et al.* (1955), Robinson (1955) and Lubowe (1955) have accumulated data describing the therapeutic efficiency of the 9a-compound (referred to throughout this article as fluorohydrocortisone) when applied topically to the skin in the relief of pruritus ani and pruritus vulvae, dermatitis venenata and certain neurodermatoses. This paper deals with the clinical evaluation of the effects of fluorohydrocortisone ointment in 129 patients with various dermatological disorders in all of which an inflammatory component was present. A comparison is made between fluorohydrocortisone ointment and hydrocortisone ointment.

Method of Observation.

In the study fluorohydrocortisone was made up in a strength of 0.1% in a base consisting of 95% liquid paraffin and 5% polyethylene (Plastibase). This base is a gel and the liquid paraffin is probably mobile within its structure. This mobility is believed to allow the active agent to migrate to a constantly changing interface, so facilitating release. The hydrocortisone was made up in a strength of 1.0% in a base consisting of liquid paraffin, soft paraffin and lanolin. The diseases investigated were divided into two groups. Group I consisted of 72 cases of pruritus ani and pruritus vulvae and Group II 57 cases of infantile eczema, contact dermatitis and flexural prurigo. All patients were ambulatory and were instructed to apply the ointment three times daily. In order to minimize personal factors in assessment of results it was arranged that only the person giving out the ointments (a registrar in one hospital and dispensers in two other hospitals) should know whether fluorohydrocortisone, hydrocortisone or dummy base had been supplied. All containers were identical and in the paired comparison study were labelled "For use on the right side" or "For use on the left side". Assessments were made weekly by the writer, who did not know which preparation was being applied.

Group I.

Several of these patients were the subject of an earlier assessment of hydrocortisone ointment (Portnoy, 1955). In the former study they were treated at first with 2.5% hydrocortisone ointment but quickly "weaned" on to the 1.0% strength if improvement occurred.

Results in this group are classified as "Excellent", meaning marked relief from irritation, "Good", where moderate relief was obtained and "Poor", in which irritation was not relieved at all. The duration of therapy averaged six weeks but final assessments were carried out at four weeks. In this group the paired comparison method could not be used but dummy base was given in twenty cases. It was arranged that the control cases should be about a quarter of the total but they were otherwise selected at random.

*Results.*TABLE I.—*Fluorohydrocortisone Ointment 0.1%.*

	Total.	Excellent.	Good.	Poor.
Pruritus ani .	40	24	3	13
Pruritus vulvae .	12	6	2	4
Totals .	52	30	5	17

"Excellent" = 57%. "Excellent" plus "Good" = 67%.

TABLE II.—*Control Base.*

	Total.	Excellent.	Good.	Poor.
Pruritus ani .	14	1	3	10
Pruritus vulvae .	6	1	1	4
Totals .	20	2	4	14

"Excellent" = 10%. "Excellent" plus "Good" = 30%.

TABLE III.—(Portnoy, 1955) *Hydrocortisone Ointment 2.5% → 1.0%.*

	Total.	Excellent.	Good.	Poor.
Pruritus ani .	56	26	9	21
Pruritus vulvae .	20	8	6	6
Totals .	76	34	15	27

"Excellent" = 44%. "Excellent" plus "Good" = 64%.

The 72 patients in Group I varied considerably in severity and duration of symptoms. Five had had the disease for more than 15 years, 6 for more than 10 years, 19 for more than 5 years, 33 for more than one year and 9 for less than one year. All could be classified as moderate or severe and more than half had had x-ray therapy. As in the group treated with hydrocortisone ointment, improvement in the "Excellent" group was dramatic and relief was usually obtained within 24 hours: similarly, if there was no improvement in the first week of treatment, the ointment usually did not help at all. Of the 35 patients who improved in Table I, 29 had prompt recurrence of irritation within 24

hours of stopping treatment. This coincides with the experience of the patients analysed in Table III (Portnoy, 1955). In the series of cases in Table I, control ointment was substituted, unknown to the patients, for the active ointment in eight of the "Excellent" group with a recurrence of irritation within 24 hours; this was relieved in each case by applying the active ointment once more. This also coincides with the results of using hydrocortisone ointment in the previous study. In those patients who relapsed promptly on cessation of therapy in Table I it was found that hydrocortisone ointment could be substituted satisfactorily for fluorohydrocortisone ointment.

Group II.

This series of 57 patients with infantile eczema, contact dermatitis and flexural prurigo was made up only of cases in which there were lesions on both sides of the body so that a paired comparison study might be made. The results tabulated below are assessed on a three-week therapy basis in those patients with infantile eczema and flexural prurigo and on a one-week basis in those with contact dermatitis. The fluorohydrocortisone ointment was applied to one limb and the hydrocortisone ointment to the opposite limb whenever possible. Where the limbs were not involved opposite sides of the body were used in sites of a symmetrical nature. Results are shown in Table IV.

TABLE IV.

	Total	(i)	(ii)	(iii)	(iv)	(v)
Infantile eczema	36	3	5	14	11	3
Contact dermatitis	12	—	2	7	2	1
Flexural prurigo	9	2	3	—	4	—
Totals	57	5	10	21	17	4

- (i)—Fluorohydrocortisone much better than hydrocortisone.
(ii)—Fluorohydrocortisone slightly better than hydrocortisone.
(iii)—Both equally effective.
(iv)—Both equally ineffective.
(v)—Fluorohydrocortisone not as good as hydrocortisone. 40 patients of the total of 57 (70%) showed improvement using either ointment.

TABLE V.—(Portnoy, 1955) *Hydrocortisone Ointment* 2.5% → 1.0%.

	Total.	Excellent.	Good.	Poor.
Infantile eczema	50	20	6	24
Contact dermatitis	10	4	4	2
Flexural prurigo	9	2	2	5
Totals	69	26	12	31

Analysis of Results.

It appears from this study that 9a-fluorohydrocortisone is at least ten times as effective therapeutically as hydrocortisone when applied topically in certain

dermatoses. The differences in action between the two compounds is quantitative and not qualitative and the response is apparently identical if adequate concentration of either substance is used. The results showed a slight therapeutic bias towards 9 α -fluorohydrocortisone in a 0.1% concentration as against 1.0% hydrocortisone. With both substances benefit in those cases which responded was usually maintained only for as long as they were applied. Their chief value lay in the rapid relief of itching with subsequent reduction in trauma.

No cutaneous or systemic reactions were noted in any of the patients treated. Thirty-eight had regular blood counts carried out but none showed any significant alteration in the number of circulating eosinophil cells. However, Livingood *et al.* (1955) have shown that under certain conditions there is significant percutaneous absorption of 9 α -fluorohydrocortisone when it is applied topically. This absorption depends in general upon the size of the area treated, the type of vehicle used and the condition of the skin at the time of application. Lotions were found to permit increased absorption compared with ointments and these workers have pointed out that the anogenital areas because they are "thin-skinned" and intertriginous are particularly suited to maximum absorption. No clinical evidence of sodium retention was noted in my patients even though applications were confined to the anogenital zone in 52 cases.

SUMMARY.

A comparison has been made between the effects of 0.1% fluorohydrocortisone ointment and 1.0% hydrocortisone acetate ointment in 129 patients with pruritus ani, pruritus vulvae, infantile eczema, contact dermatitis and flexural prurigo.

The fluorohydrocortisone ointment has an effect at least as good as that of 1.0% hydrocortisone acetate ointment.

The difference in action between the two compounds appears to be quantitative and not qualitative.

No undesirable local or systemic effects were noted.

My thanks are due to Messrs. E. R. Squibb and Sons for supplies of Florinef Ointment and Plastibase.

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OXFORD REGIONAL DERMATOLOGICAL GROUP.

Northampton, 18 February 1956.

Dermatomyositis with Secondary Calcification.—Dr. R. WIGGLESWORTH and Dr. R. B. COLES.

This girl, now aged 8, was well until May 1951, when she began to complain of listlessness, anorexia, and back-ache. The face, fore-arms and hands were swollen and skin changes rapidly developed. The clinical diagnosis of dermatomyositis was made in September 1951. Muscle and skin biopsies taken at this time supported the diagnosis.

In 1952 calcium deposits began to develop. Some of these were entirely subcutaneous but others were present in the deep fascia and in intermuscular planes, and added to the restriction of movement that was already present. There was some ulceration of deposits through the skin.

In 1954 the spleen became palpable. A barium swallow was normal and the E.S.R. remained normal.

Treatment and progress.—The patient has had extensive steroid treatment and physiotherapy. Recently she has improved and the calcified plaques have become fewer, particularly in the upper part of the body. Greater freedom of movement has been gained. Some of the calcified lesions have ulcerated through the skin but many seem to have dissolved spontaneously. The skin changes, which were very marked at first, are now very much less obvious.

Comment.—The case is shown because of the remarkable tendency for the calcification to disappear. Parkes Weber (1947) calls attention to the tendency of calcinosis universalis in young girls to improve and he quotes Kennedy's case (1932) of calcinosis and sclerodermia, in which calcareous deposits partly disappeared during treatment with a ketogenic diet.

In a total of 78 cases of calcinosis universalis mentioned by Atkinson and Parkes Weber (1938), 25 had sclerodermia.

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2nd edition, 79.

Juvenile Acanthosis Nigricans.—Dr. I. S. HODGSON-JONES.

A surveyor aged 21 years.

This patient has noticed progressive horniness of the left palm since the age of 15 years. His skin always had a tendency to be rough and hard in some places.

On examination he shows pigmentation and fissuring around the angles of the mouth: both axillae are hyperkeratotic and hyper-pigmented, and the left palm is thickened and fissured. The groins and soles are unaffected and the right palm shows only slight thickening. There is no evidence of this abnormality having occurred in the family before.

The general appearance of the patient is unusual: He is dwarf-like with a large skull, and appears unduly old for his age. The picture resembles progeria. Mentally he is alert. Otherwise, he is normal and there is no evidence of carcinomatosis.

Histology.—The skin shows acanthosis and melanosis.

It is considered that he is suffering from benign acanthosis nigricans of the juvenile type which—like some of the cases described by Kemerl (1937) and mentioned by Sheldon and Curtis (1955)—is associated with chondrodystrophy and dwarfism.

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The following cases also were shown :

Xanthoma Tuberosum Multiplex (3) ; **Epidermolysis Bullosa Dystrophica** ; **Urticaria Pigmentosa** (2) ; **Adenoma Sebaceum with Subungual Fibromata** ; **Mycosis Fungoides** ; **Scleroderma** (2) ; **Naevi** (2) ; **Dermatomyositis** (2) ; **Pemphigus Vegetans** ; **Pretibial Myxoedema** ; **Necrobiosis Lipoidica** (non-diabetic) ; **Benign Familial Pemphigus** (Hailey-Hailey) ; **Unilateral Rosacea**.

NORTH OF ENGLAND DERMATOLOGICAL SOCIETY

Manchester, March 1956.

Osteoma Cutis.—Dr. G. AUCKLAND.

A man aged 25.

History.—At the age of 5 his mother first noticed that he had “ lumps ” at the back of his neck. There is no discomfort except that recently the skin became red and tender over one area on the right side of the neck.

Past history.—No acne or haemangiomas.

Family History.—Nil relevant.

Examination.—Numerous hard painless subcutaneous nodules are easily felt just below the skin surface at the back of the neck and extending around the sides of the neck as far as the mastoid process.

Investigations.—Blood calcium 11.5 mg.%. Blood W.R. and Kahn, negative. Skiagram of neck shows about 20 opaque masses in the soft tissues posterior to the cervical vertebrae, varying in size from 0.1 cm. to 1.5 cm. in diameter. All are clearly defined and most are spherical or ovoid in shape. The largest have an irregular outline and are not uniform in opacity.

Histology.—The epidermis is normal. In the corium there is a mass consisting of trabeculae of compact bone surrounded by fibrous tissue in which normal arterioles and thin walled vessels are present.

Comment.—This seems to be an example of primary (heterotopic) bone formation. The bone probably develops from embryonal rests and can be regarded as a bony naevus or hamartoma.

Grease Gun Granuloma.—Dr. J. G. COBURN.

A man aged 42.

History.—The patient was first seen five months ago, shortly after having injured the skin at the base of the left 5th finger with a jet from a high-pressure grease gun. The jet of grease having penetrated the skin, a swelling 1½ inches in diameter appeared and there was some associated limitation of movement at the knuckle joints.

The opening in the skin gradually healed but two months after he was first seen it broke down again, and since then there has been an intermittent discharge of debris from this hole.

Examination.—The swelling is now $\frac{3}{4}$ inch in diameter and the hole is gradually closing, although there is still some discharge from it.

Comment.—Although this does not appear to be a common condition, the patient himself was familiar with it. Satisfactory resolution is taking place without treatment and there is every reason to suppose that the lesion will eventually disappear completely.

Norwegian Scabies.—Dr. MORGAN for Dr. WILKINSON and Dr. MUMFORD.

A woman aged 18 years.

History.—Fifteen months ago this patient developed purple patches on the legs, which later also appeared on the hands and face. Apart from vague rheumatic pains she felt well.

She was admitted to a hospital elsewhere with the diagnosis of acute lupus erythematosus. At this time she was found to have marked anaemia and leucopenia. On treatment with cortisone the skin eruption apparently subsided sufficiently for her to be discharged, but she was later re-admitted.

Nine months ago the skin eruption became more widespread and took on a scaly and hyperkeratotic character. She also developed numerous pyodermic lesions and these have continued since. In view of the gravity of her anaemia, and the continuing rash and general debility, she was transferred to Manchester under the care of Dr. Wilkinson.

She gives no history of members of her family suffering from itching but it has not been possible to examine them all. No member of the medical or nursing staff here, or at the previous hospital, has so far been affected.

Examination.—There is a generalized scaly papular eruption, affecting all areas including the head and neck. On the hands, elbows, eyebrows, and knees, these lesions have agglomerated into grossly hyperkeratotic plaques. There is gross dystrophy and hyperkeratosis of the nails. Scattered on the limbs are several boils and septic areas. She has some itching.

She continues with a grave anaemia, leucopenia, and with abnormal reticulum cells in the marrow and in the peripheral blood. There is no other abnormality on general physical examination. The haematological diagnosis is "reticulum-celled leukaemia" and for this she has been receiving transfusions. The eruption was not immediately recognized as crusted scabies but a biopsy was made and it was on this histological picture that the diagnosis was recognized.

Histology.—The section shows numerous burrows in a thickened horny layer. Scraping reveals multitudes of acari, nymphae and ova.

Investigations.

Blood. 20.ii.56.

Hb. 36%. RBC. 1,790,000 per cu.mm. WBC. 3,000 per cu.mm. (polys. 37%, lymphs. 34%, monos. 6%, eos. 1%, "blasts" 22%).

5.iii.56(after transfusion).

Hb., 60%. RBC. 3,510,000 per cu.mm. WBC. 1,400 per cu.mm. (polys. 27%, lymphs. 22%, monos. 2%, eos. 4%, "blasts" 42%, plasma 3%).

E.S.R. 72.

Serum Proteins: Albumen 2.8 g.%; globulin 4.0 g.%.

Postscript.—On treatment with benzyl benzoate the eruption has cleared up very quickly except for the hyperkeratotic dystrophy of the nails.

Granuloma of Face.—Dr. MORGAN (for Dr. DAVIES).

A retired electric fitter aged 69 years.

Onset two years ago after attack of pneumonia.

Chronic, nodular and ulcerative lesion commenced on left cheek, progressing peripherally, and healing by scarring in centre. In the past year a similar process

has affected the right malar region and right eyelid, and the right angle of the mouth. Fresh active areas have continued to occur, mainly on right side of face.

Past history.—Chronic bronchitis for many years. (The expectorant mixture he has taken has not contained iodides.)

Examination.—Puckered sclerosis and scarring of the left cheek, with translucent yellow nodules in the scar. On the right side of the face is a more active process, with soft nodules and scarring, extending up to the eyelids. These show now only a chronic erythema. At present none of the lesions is ulcerated. There is a crusted reddened area at the right angle of the mouth.

There are no mucosal lesions and no enlarged glands.

General examination.—He has mild emphysema. B.P. 185/100; otherwise normal.

Investigations.—W.R. negative. Urine normal. Blood: Hb. 98%. WBC. 10,400 per cu. mm. (polys. 63%, lymphs. 32%, monos. 5%).

Mycology: No evidence of deep mycosis on culture of tissue material.

Skiagrams of chest and sinuses.—Normal.

Histology.—There is moderate acanthosis overlying a chronic inflammatory infiltrate, which consists of lymphocytes and plasma cells, with a few foreign-body giant cells. In the upper part of the dermis there is some hyalinization of the collagen. The picture is that of a non-specific granuloma.

Comment.—No firm opinion on the aetiology of this granuloma has been reached. The possibility of artefact has been considered.

Congenital Ectodermal Defect. Atrophoderma Vermicularis with Leukokeratosis Oris.—Dr. SEVILLE and Dr. MUMFORD.

History.—The patient has had a sore mouth and a rash on his face since he was four months old. He attended hospital in 1952 because of nasal obstruction since birth, diagnosed as "nasal catarrh". In December 1952 a seborrhoeic rash was noted in the Eye Department causing blepharitis.

Early in 1954 he was admitted to hospital for treatment of anaemia (Hb. 51%, C.I. 0.74) with penicillin and iron. He was discharged with Hb. 71%, C.I. 0.71. His tuberculin jelly test was positive and Mantoux 1/100 repeatedly negative. It was concluded that there was no evidence of any tuberculous infection. The nasal catarrh cleared following adenoidectomy in February 1954.

On examination.—Erythematous areas are present on the face particularly on the cheeks, with minimal telangiectasia, follicular crusting, and fine pitted scars. A seborrhoeic retroauricular fissure is noted on the left side.

A milky white sheen is present on the tongue with fissures on the buccal mucous membrane. This is especially seen in a band opposite the dental edges and extending on to the soft palate.

Investigations.—Wassermann reaction negative. Repeated cultures from the mouth gave no monilia.

Treatment.—Siccolam, neomycin and hydrocortisone ointment, or systemic cortisone (50 mg. daily for 2 weeks, 75 mg. for 1 week, 50 mg. for 1 month and 25 mg. for 2 weeks) clears the seborrhoea, but nothing has had the slightest effect on the mouth, including the repeated use of gentian violet paint.

A course of diodoquin suggested in the discussion had no beneficial effect.

CURRENT LITERATURE.

CONTAGIOUS DISEASES OF ANIMALS AND MAN. I. MARTIN-SCOTT. (1955) *Vet. Record*, **67**, 883.

This is a review article which does not lend itself to abstracting. The author covers a great deal of ground and concisely summarizes a large number of diseases which are common to animals and man. There are some useful references and the article contains sufficient information to make it of value itself for reference purposes.

F. R. B.

MORBILLIFORM RASHES. Z. MONCRIEFF. (1955) *Med. Pr.*, **234**, 41.

This article deals only with morbilliform rashes in children. Conditions in which such rashes occur are measles, rubella, toxic states, drugs and serum administration, roseola infantum (exanthem subitum), erythema toxicum (a variant of erythema multiforme), roseola vaccinalis and erythema infectiosum.

Each of these conditions is described adequately; the difficulties of differential diagnosis are stressed and those who are confronted with these often puzzling cases are advised to read the original article.

H. R. V.

MALIGNANT DISEASES OF THE SKIN. I. S. HODGSON-JONES. (1955) *Med. Pr.*, **234**, 267.

The generally accepted views on rodent ulcer, squamous epithelioma and melanomata are given. As this article is written primarily for general practitioners the author rightly stresses the diagnosis and treatment of kerato-acanthoma. He prefers complete excision to other forms of therapy of this condition.

H. R. V.

THE CONTRIBUTION OF MYCOLOGY TO MEDICINE. R. W. RIDDELL. (1955) *Med. Pr.*, **234**, 217.

This excellent article gives a complete summary of the present position of fungi pathogenic to man. Fungous infections are considered under the headings, superficial, subcutaneous, pulmonary and systemic.

A great deal of research has been done on this group of organisms in recent years and differences in the clinical behaviour of different types depend on such factors as natural habitat, the type of keratin, disulphide linkages and hydrogen bonds, the fungicidal and fungistatic fatty acids of the sebum, whether or not hair is in the resting state, the sex of the patient, etc.

Subcutaneous, pulmonary and systemic infections are uncommon in this country, but the author wonders whether increasing use of antibiotics will increase their incidence.

H. R. V.

OTITIS EXTERNA. D. A. T. FARRAR. (1955) *Med. Pr.*, **234**, 29.

Otitis externa is common and, unless treated adequately, may be very persistent. The common causes are furunculosis, diffuse purulent infection, seborrhoeic dermatitis, eczema and sensitivity reactions. Less common are haemorrhagic bullous otitis externa and herpes zoster otitis.

Furuncles respond to local treatment and systemic antibiotics, although vaccines may be necessary in recurrent cases. Of the diffuse purulent infections *P. pyocyanea* must be remembered; this is sensitive to polymyxin B given usually as drops of the 10% solution of the sulphate. Seborrhoea is treated along accepted lines. Attention must be paid to the scalp, and in eczema, calamine liniment, glycerine of ichthammol, 10% silver nitrate solution and Lassar's paste all have their place.

In the author's experience at present chloramphenicol is the most common cause of a sensitization eruption, although reactions also occur to penicillin, streptomycin, sulphonamide, flavine and iodine. Prevention of recurrence is particularly important after recovery from otitis externa. The areas must be kept dry—if necessary, vaselined cotton wool plugs should be used during hair washing, etc.

H. R. V.

PRURITUS VULVAE. F. H. FINLAISON. (1956) *Med. Pr.*, **235**, 194.

Pruritus is a symptom due to many different causes. In this paper only those causes peculiar to the vulva are considered. In a gynaecological clinic the great majority of cases of pruritus

vulvae are due to infection with either trichomonas or monilia. In both these infections it is necessary to continue to treat the condition over several months, since relapses are common at the menses.

For trichomonas the vagina is swabbed clear of discharge and painted with an antiseptic such as 2% gentian violet in water, silver dinaphthylmethane disulphonate 1% (Viacutan) or mercury in organic combination (Penotrane). Afterwards pessaries containing acetarsol are used.

For monilial infections, the vagina is painted as above.

Other conditions to be considered are tinea cruris, scabies and pediculosis pubis.

Degenerative conditions of the vulva—kraurosis, leukoplakia, and lichen sclerosus—often give rise to intense irritation, but there is still some diversity of opinion over the precise definition of these conditions. Deficiency states, such as anaemia and achlorhydria, are sometimes associated with pruritus vulvae, and occasionally this is a symptom of vitamin A or vitamin B deficiency.

Psychological stress is frequently present, although it is not always easy to be certain which came first, the stress or the itch. H. R. V.

SODIUM RETENTION AND EDEMA FROM PERCUTANEOUS ABSORPTION OF FLUDRO-CORTISONÉ ACETATE. T. B. FITZPATRICK, H. G. GRISWOLD and J. H. HICKS. (1955) *J. Amer. med. Ass.*, **158**, 1149.

After experiments had failed to demonstrate any evidence of absorption of 2½% hydrocortisone acetate lotion, fludrocortisone acetate lotion and ointment were similarly evaluated. Evidence of sodium retention was observed in 20 patients after topical applications of this drug. Percutaneous absorption diminishes as the dermatitis improves. The sodium retention might be hazardous in certain patients. A. J. R.

ECTODERMAL DYSPLASIA PRESENTING AS FEVER OF UNKNOWN ORIGIN. F. C. STYLES and J. R. WEIR. (1955) *J. Amer. med. Ass.*, **158**, 1432.

A white boy, aged 11 months, ran an unexplained fever intermittently from the first weeks of life. Observation in hospital demonstrated the correlation between the fever and the environmental temperature. This child also showed the symptoms of laryngitis, which, together with those of chronic rhinitis, have been noted in other cases with ectodermal dysplasia of the anhidrotic type. A. J. R.

FEASIBILITY OF SKIN TESTING FOR PENICILLIN SENSITIVITY. A. J. BERGER and B. EISEN. (1955) *J. Amer. med. Ass.*, **159**, 191.

Scratch, patch and intradermal tests with penicillin were carried out in 1000 individuals in 3 groups: "allergic", "non-allergic" and those known to be sensitive to penicillin. There was no correlation between the results of the tests and the presence of penicillin sensitivity. Great attention must therefore be paid to a history of previous reactions. A. J. R.

PROBLEM OF ECZEMA. R. BOOKMAN. (1955) *J. Amer. med. Ass.*, **159**, 1275.

The author, an allergist, is concerned with atopic dermatitis. He attempts to reanimate hypotheses which many dermatologists consider moribund. His own summary follows:

"Eczema, or allergic dermatitis, is not a problem if it is regarded as a skin manifestation of allergy intensified by prolonged scratching. Symptomatic relief of itching is most effective when simple medication is used. Certain practices such as patch testing and elimination diets are found to be of little value in handling eczema. The ultimate goal of therapy is discovery and treatment of specific causes. These are determined by a careful history corroborated by skin testing."

A. J. R.

COMMITTEE ON COSMETICS. TREATMENT OF ACNE SCARS BY DERMABRASION. J. RATTNER and C. R. REIN. (1955) *J. Amer. med. Ass.*, **159**, 1299.

As the abrasion treatment of acne scars has received considerable attention in both medical and lay press recently this report to the Committee on Cosmetics of the A.M.A. is timely. The rotary-brush technique is described. Selection of cases is important; the superficial flat scars respond best, deep and narrow and wide confluent scars less well. With care in selection of patients, "in general the majority of patients are satisfied with the results. The treatment does not produce miraculous new skin."

A. J. R.